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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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[REDACTED] ART UNIT [REDACTED] PAPER NUMBER

1637

DATE MAILED: 11/06/2002

12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/885,731	ERIKSON ET AL.	
	Examiner	Art Unit	
	Suryaprabha Chunduru	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 04 September 2002.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-55 is/are pending in the application.
- 4a) Of the above claim(s) 28 and 30-55 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-27 and 29 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) Notice of References Cited (PTO-892)
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
- 4) Interview Summary (PTO-413) Paper No(s) _____.
- 5) Notice of Informal Patent Application (PTO-152)
- 6) Other: _____

DETAILED ACTION

1. The Information Disclosure Statement (Paper No. 7) filed on December 7, 2002 has been entered and considered.
2. Applicant's election with traverse of Group I in Paper No. 11 is acknowledged. The traversal is on the ground(s) that examining all groups would not be a serious burden, since search for art relating to one group would result in art relating to each of the other 4 groups. This is not found persuasive because of the following reasons: (i) search for one group not necessarily result in art related to another group (ii) separate classification search is *prima facie* evidence of burden, (iii) the issues are not the same with respect to 35 U.S.C. 112 and 35 U.S.C. 101 statutes, (iv) separate Art units would examine the two Groups under ordinary circumstances. Hence the restriction requirement is still deemed proper.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-63 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

“ factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims”.

The nature of the invention

Claims 1-27 and 29 are drawn to a method comprising formation of a multiplex structure involving Watson-Crick base pairing rules with each of the strands in relation to all other strands that is, more than two strands are adhered to each other obeying Watson-Crick base pairing rules and with dependent claims further limiting conditions in the formation of multiplex structure. The invention is a class of invention, which the CAFC has characterized as “the unpredictable arts such as chemistry and biology.” *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed.Cir.2001).

The Breadth of the claims

The claims encompass a comprising a method of creating multiplex structure involving Watson-Crick base paring with more than two strands. The specification does not provide any

structure formation of multiplex with the specific Watson-Crick base pairing among the nucleic acid strands.

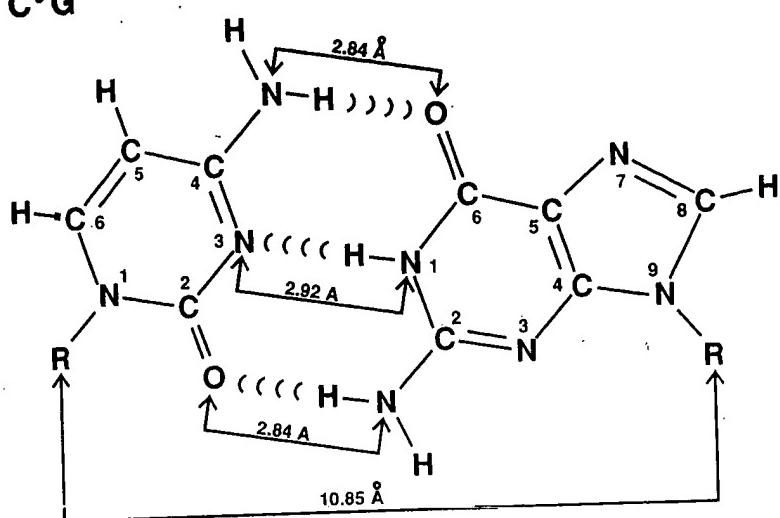
Quantity of Experimentation

The quantity of experimentation in this area is extremely large since structural identity of the multiplex structure of nucleic acid would initially require, in vitro studies to demonstrate proof of principle. That is, prior to any structural intervention, it would be necessary to create a crystallographic or NMR (nuclear magnetic resonance) structure, show that the structure occurs in sufficient stability and then show stability of the structure is associated with Watson-Crick base pairing with more than two strands, a series of showings not present in the specification. Following such experimentation, the multiplex structure of nucleic acids would need to be characterized and stability of the structure would need to be demonstrated. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction of practice, not providing any guarantee of success in the succeeding steps.

The unpredictability of the art and state of art

Predictability in the art suggests interaction of two strands in a duplex involves Watson-Crick bonding. Hydrogen bonding and base stacking hold a duplex DNA helix together as shown in the following Fig. 1.7.

C·G



A·T

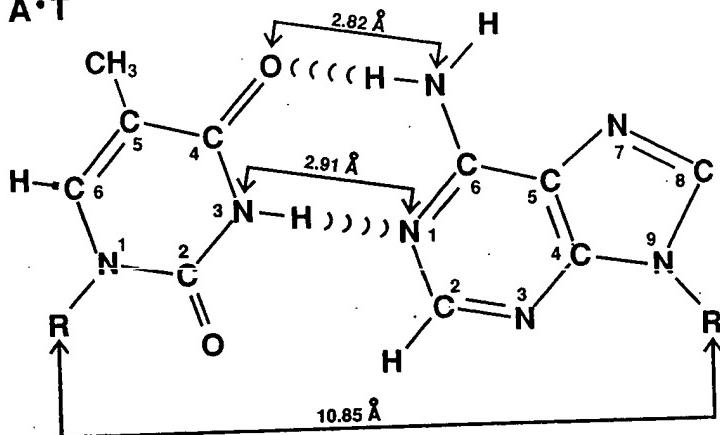


Figure 1.7 Watson-Crick base pairs. The interatom hydrogen bond distances and distances between the C1' positions of the ribose sugars are indicated. The curved lines represent the hydrogen bonds. The curves are in the direction of the hydrogen bond acceptor (N or O atoms). Figure modified with permission from Arnott *et al.* (1965).

As shown in the Fig 1.7, a hydrogen bond is a directional interaction between a covalently bound H atom and a nitrogen or oxygen of a base (adenine (A), thymine (T), Guanine (G), cytosine (C)). In the C.G base pairing it is apparent from the figure that the middle N-H hydrogen bond would be inaccessible for any other strand for Watson-crick pairing. A reverse Watson-crick base pairing occurs when one nucleotide rotates 180° with respect to complementary nucleotide. This type of base pairing is found in Hoogsteen base pairing. The

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instant specification does not provide any pictorial or space-filling model to show the Watson-Crick paring in the multiplex structure.

Further, it is also evident from the prior art that Watson-Crick double helix structure of DNA (B-form) is right handed and the common form, originally deduced from X-ray diffraction analysis. As shown in the Fig. 1.14 A and B below, a dominant feature of B-form DNA is the presence of major and minor grooves. Different functional groups on the purine and pyrimidine base are accessible from major or minor grooves. The Watson-Crick hydrogen bonding surfaces are not available to solvents or proteins, since functional groups involved in hydrogen bonding are interacting with each other at the center of the double helix. The hoogsteen bonding surface of purine is accessible through major groove. It is apparent from the figure that the Watson-crick hydrogen bonding surfaces are inaccessible for any other strands since two strands are already interacting with each other at the center of the double helix.

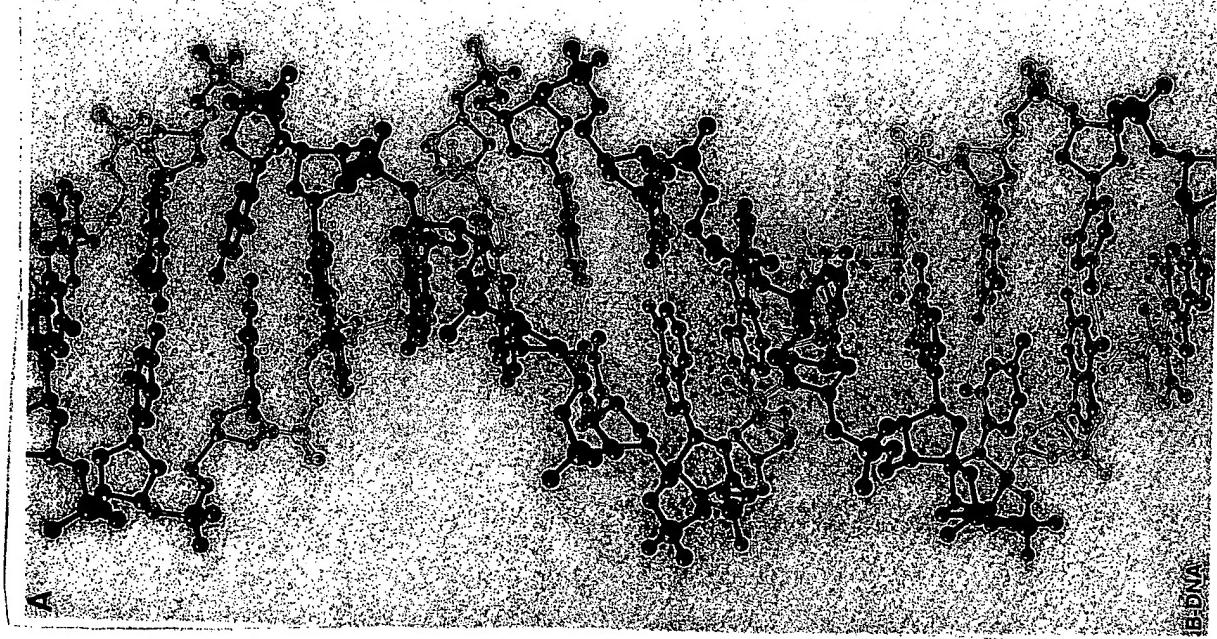


Figure 1.14 B-DNA helix. (A) In this model of the B-DNA helix the phosphate backbones can be seen as smooth right-handed coils on the outside of the helix. This view looks into a minor groove at the center of the model. Major grooves are seen above and below the minor groove. (Copyright by Irving Geis.)

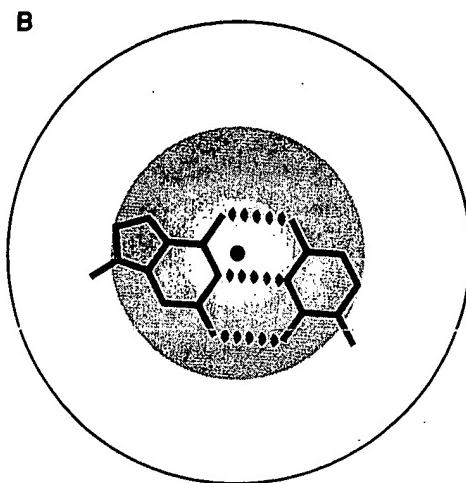


Figure 1.14 *Continued.* (B) In the B-DNA helix the hydrogen bonded base pairs are stacked near the center of the helix. The center of the helix passes nearly symmetrically through the Watson-Crick

The prior art also indicates that the triple helix does not represent the most thermodynamically stable structure that can be adopted by two complementary poly purine, poly pyrimidine strands. There is a loss of Watson-Crick hydrogen bonding in a triplex DNA formation (see page 225, Fig 6.4 and paragraph 1).

The instant specification, would not be easily translatable to (i) the multiplex structure formation with a single hydrogen bond interacting with more than two strands utilizing Watson-Crick base pairing; (ii) crystallographic or NMR predicted model for the multiplex structure of the claimed invention. The unpredictability of multiplex structure is evidenced by the prior art,

which fails to support Watson-Crick base pairing in triplex formation and in fact support unpredictability of this area of technology.

Working Examples

The specification failed to show any working examples regarding physical structure based on crystallography or NMR model or X-ray diffraction analysis for multiplex structure. The Exhibit C in the specification show the fluorescent intensity as a function of binding affinity between target and probe strands, but do not provide any evidence for the physical structure for the multiplex structure with Watson-crick base pairing among the multiple strands of nucleic acids.

Guidance in the specification

The specification, while providing a general review of various nucleic acid structures, does not provide teachings sufficient to overcome doubts raised in the art with regards to the stability of multiplex structure. No specific teachings regarding the use of multiplex structure in assaying triplex and quadruplex nucleic acid complexes. It would be essentially be a trial and error process, to make and use of the diverse species of multiplex structure of nucleic acids encompassed by the claims. No space filling model or structural model of the interaction involving Watson-Crick base pairing with more than two strands is provided.

Level of skill in the art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, the level of unpredictability is high, the specification provides no written description or guidance that leads one to a reliable or stable

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multiplex structure. One skilled in the art cannot readily anticipate the effect of change within the subject matter to which the claimed invention pertains. Further the specification does not provide guidance to overcome art recognized problems in multiplex structure formation. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance and direction provided in the specification, the absence of any working examples and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claimed invention as broadly written.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7 and 23 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 7 and 23 are confusing for referring to the subject matter in the term "and/or". Thus it is unclear how the claims can simultaneously encompass all of these limitations. The claims should refer to the subject matter in the alternative only, the replacement of the term "and/or" with "or" or the addition of dependent claims are suggested.

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686

F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-27 and 29 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 8-9, 17-18, 20, 24, 26-27, 29-30, 32-37 of U.S. Patent No. 6,420,115. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims recite a method of creating a nucleic acid multiplex (a duplex or triplex or quadruplex) said method comprises (i) creating a mixture comprising water (liquid medium), a Watson-Crick duplex, a single-stranded mixed base sequence (a, probe, partially complementary to the target) and an accelerator (a cation or intercalator), (ii) incubating the mixture to allow to form a multiplex. The patented claims encompass these limitations in the instant claims. The instant claims and the patented claims differ only in recitation of the method as ‘a method of creating a nucleic acid multiplex’ which is an obvious variation of the method disclosed as ‘a method for assaying binding, and formation of a triplex’ in the patented claims. The recitation of water in the instant claims is obvious over the patented claims, which recite ‘a volume based medium’. The G-C content between 10% and 90% recited by the instant claims were encompassed in the patented claim 36. Thus the patented claims encompass the limitations recited in the instant claims. Therefore the instant claims are rejected under obviousness-type double patenting.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-2, 18-22 are rejected under 35 U.S.C. 102(e) as being anticipated by Fresco et al. (US, 6,461,810).

Fresco et al. teach a method of forming a nucleic acid multiplex structure wherein Fresco et al. teach that the method comprises (2) contacting in a hybridization buffer, a double-stranded nucleic acid with a third strand (an oligonucleotide probe, single-stranded), (ii) and incubating the mixture under hybridization conditions to allow formation of a multiplex structure (see column 1, lines 56-67, column 4, lines 22-26, column 3, lines 19-47). Fresco et al. also teaches that the method comprises (i) an intercalator (such as acridine, psoralen) as an accelerator agent (see column 5, lines 17-38); (ii) non-intercalator (such as biotin conjugated probes) as an accelerator (see column 9, lines 7-15). Thus the disclosure of Fresco et al. meets the limitations in the instant claims.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suryaprabha Chunduru whose telephone number is 703-305-1004. The examiner can normally be reached on 8.30A.M. - 4.30P.M, Mon - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and - for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.


Suryaprabha Chunduru
October 25, 2002


JEFFREY FREDMAN
PRIMARY EXAMINER